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Journal Article

Potential use of bisphosphonates in children with Legg–Calvé–Perthes disease with signs of osteoarthritis. Interim results from a single-center study

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ABSTRACT

BACKGROUND: The Legg–Calvé–Perthes disease is a multifactorial disease with a noninflammatory and avascular process of necrotic lesion development. In some cases, children may have a more aggressive disease with signs of osteoarthritis. This variant of the Legg–Calvé–Perthes disease is characterized by active inflammation of the bone tissue and arthritis, often leading to severe deformity of the femoral head and early coxarthrosis. The problem of treating osteoarthritis in children with the Legg–Calvé–Perthe disease is still unaddressed because of the low effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs). Osteoclast inhibition therapy with bisphosphonates in adults with idiopathic aseptic necrosis of the femoral head has been pathogenetically accepted. However, the use of bisphosphonates in children with the Legg–Calvé–Perthe disease and osteoarthritis has not been evaluated.

AIM: This study aimed to evaluate the efficacy and safety of bisphosphonates in children with the Legg–Calvé–Perthes disease who presented with signs of osteoarthritis.

MATERIALS AND METHODS: The study used data on the treatment of 14 children (mean age, 7.5 ± 2.4 years, 71.4% girls) with the Legg–Calvé–Perthe disease at the impression fracture stage and active hip osteoarthritis. All children had torpid arthritis refractory to NSAID therapy, which was present for at least 3 months. Treatment included ibandronic acid 1.0 mg and 1.5 mg per infusion every 3 months in children aged <7 and >7 years, respectively. Five consecutive infusions were performed. Treatment outcomes were assessed at 6, 12, and 18 months based on the combined clinical, imaging, and laboratory changes. A modified SCORING OF HIP MRI FOR JIA score was used to assess osteoarthritis activity.

RESULTS: All children experienced diminished hip pain after the first infusion of ibandronic acid. During bisphosphonate therapy, the inactive phase of osteoarthritis was achieved in 78.5% (11) of the children after three consecutive infusions and 21.5% (3) after four infusions. Post-infusion reactions were reported in 85.7% (12) of the children during the initial phase of bisphosphonate therapy and were transient. The serum erythrocyte sedimentation rate, C-reactive protein, interleukin-6, and tumor necrosis factor-alpha levels were within the reference ranges in children with osteoarthritis. Only 28.5% (4) of the patients were found to have 25(OH) vitamin D deficiency upon osteoarthritis diagnosis.

CONCLUSIONS: The use of bisphosphonates in children with the Legg–Calvé–Perthes disease and osteoarthritis can be an innovative pathogenetic treatment option. The data suggest the potential use of bisphosphonates in children with the Legg–Calvé–Perthes disease. Further follow-up of children in the study group is needed to assess long-term outcomes.

Keywords: aseptic necrosis of the femoral head; Legg–Calvé–Perthes disease; synovitis; osteoarthritis; bisphosphonates.

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Научная статья

Перспективы применения терапии бисфосфонатами у детей с болезнью Легга – Кальве – Пертеса, протекающей с признаками остеоартрита. Предварительные результаты моноцентрового исследования

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АННОТАЦИЯ

Обоснование. Болезнь Легга – Кальве – Пертеса — мультифакторное заболевание, при котором механизм формирования очага некроза носит невоспалительный аваскулярный характер. В некоторых случаях заболевание у детей протекает более агрессивно с признаками остеоартрита. Такой вариант течения болезни Легга – Кальве – Пертеса проявляется активным воспалением костной ткани и артритом, что часто приводит к выраженной деформации головки бедренной кости и развитию раннего коксартроза. В настоящее время проблема лечения остеоартрита у детей с болезнью Легга – Кальве – Пертеса не решена в связи с низкой эффективностью нестероидных противовоспалительных средств. Терапия подавления активности остеокластов при помощи бисфосфонатов у взрослых с идиопатическим асептическим некрозом головки бедренной кости признана патогенетически обоснованной. Использование бисфосфонатов у детей с болезнью Легга – Кальве – Пертеса, сопровождающейся признаками остеоартрита, не изучено.

Цель — оценить эффективность и безопасность применения бисфосфонатов у детей с болезнью Легга – Кальве – Пертеса, протекающей с признаками остеоартрита.

Материалы и методы. Основу исследования составили данные лечения 14 детей (средний возраст детей — 7,5 ± 2,4 года, 71,4 % девочки) с болезнью Легга – Кальве – Пертеса (на стадии импрессионного перелома) и активным остеоартритом тазобедренного сустава. Все дети имели артрит, торпидный к терапии нестероидными противовоспалительными средствами, длительностью не менее 3 мес. В лечении использовали ибандроновую кислоту в дозе 1,0 мг на инфузию детям до 7 лет, в дозе 1,5 мг детям старше 7-летнего возраста с кратностью введения каждые 3 мес. Исследование включало пять последовательных инфузий. Результаты лечения оценивали через 6, 12, 18 мес. на основании совокупной динамики клинических, инструментальных и лабораторных данных. Для определения степени активности остеоартрита была применена модифицированная шкала SCORING OF HIP MRI FOR JIA.

Результаты. У всех детей болевой синдром тазобедренного сустава уменьшился уже после первой инфузии ибандроновой кислоты. Неактивная стадия остеоартрита на фоне использования бисфосфонатов была достигнута у 78,5 % (11) детей после трех последовательных инфузий, у 21,5 % (3) — после четырех введений препарата. Постинфузионные реакции отмечены у 85,7 % (12) детей на начальном этапе лечения бисфосфонатами и носили кратковременный характер. Показатели скорости оседания эритроцитов, С-реактивного белка, интерлейкина-6 и фактора некроза опухоли альфа в сыворотке крови у детей с остеоартритом не выходили за рамки референсных значений. Недостаточность 25-ОН витамина D выявлена лишь у 28,5 % (4) пациентов на момент диагностики остеоартрита.

Заключение. Применение бисфосфонатов у детей с болезнью Легга – Кальве – Пертеса, протекающей с остеоартритом, можно рассматривать как инновационный патогенетически обоснованный метод лечения. Полученные данные указывают на перспективность использования бисфосфонатов у детей с болезнью Легга – Кальве – Пертеса. Требуются дальнейшие наблюдения изучаемой группы детей для оценки отдаленных результатов.

Ключевые слова: асептический некроз головки бедренной кости; болезнь Легга – Кальве – Пертеса; синовит; остеоартрит; бисфосфонаты.

Как цитировать

Кожевников А.Н., Барсуков Д.Б., Бортулёв П.И., Брайлов С.А. Перспективы применения терапии бисфосфонатами у детей с болезнью Легга – Кальве – Пертеса, протекающей с признаками остеоартрита. Предварительные результаты моноцентрового исследования // Ортопедия, травматология и восстановительная хирургия детского возраста. 2024. Т. 12. № 4. С. 463–472. DOI: https://doi.org/10.17816/PTORS636471

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ЭКО•ВЕКТОР

BACKGROUND

The Legg–Calvé–Perthes disease (LCPD) is one of the most common and severe musculoskeletal disorders in children, which often leads to coxarthrosis and loss of joint function. Its underlying mechanisms involve the formation of an avascular osteonecrosis locus, which is still unclear [1]. LCPD progresses through distinct stages, beginning with femoral head necrosis, advancing to the stage of compression fracture, and culminating in new bone tissue formation [2]. The prognosis is more favorable with timely and comprehensive treatment [3]. However, in some cases, even with appropriate therapy, the disease manifests more aggressively, characterized by osteoarthritis symptoms. This variant is marked by chronic bone inflammation and hip joint arthritis (synovitis) during the formation and peak of the osteonecrotic lesion [4]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) typically does not alter the disease course or prevent femoral head deformation [5]. Dissatisfaction with traditional treatment outcomes has driven the search for novel therapeutic models to address the progression of osteoarthritis in children with LCPD.

LCPD is the most common form of aseptic necrosis of the femoral head (ANFH) in children [6]. The prevalence of ANFH ranges from 0.4 to 29 per 100,000 children across different ethnic groups. Boys are more frequently affected, with unilateral involvement in 85%–90% of the cases [7]. Transient synovitis is a common feature during the initial stage of osteonecrosis formation in LCPD. However, in some cases, synovitis progresses to chronic arthritis with bone inflammation, its causes remain unknown [8]. A potential mechanism underlying the chronic inflammatory process in the hip joint is uncontrolled osteoclast hyperactivity within the necrotic lesion, accompanied by the hyperproduction of proinflammatory cytokines [9]. This disease variant should be regarded as osteoarthritis, for which no therapy has been established yet. Prolonged NSAID use often fails to achieve the desired effect, leading to extended disease progression [10]. Immunosuppressive therapy is not justified because the features of osteoarthritis do not meet the diagnostic criteria for juvenile idiopathic arthritis (JIA) [11]. Chronic osteoarthritis may exacerbate the necrotic lesion, result in severe femoral head deformation, and hinder timely surgical treatment because of ongoing inflammation [12]. Numerous studies have demonstrated that bisphosphonate (BP) therapy in adults with idiopathic ANFH reduces inflammation, prevents further femoral head deformation, alleviates pain, and improves hip joint function [13]. However, no clinical studies have evaluated BP therapy in children with LCPD in both the domestic and international settings [14].

This study aimed to evaluate the efficacy and safety of BP therapy in children with LCPD presenting with osteoarthritis symptoms.

MATERIALS AND METHODS

The study included 14 children (71.4% girls) with Legg–Calvé–Perthes disease presenting with signs of osteoarthritis. These patients were treated at the H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery between 2022 and 2024. At enrollment, all children were diagnosed with LCPD in the stage of compression fracture, characterized by magnetic resonance imaging (MRI) findings of trabecular bone edema and "active" chronic synovitis (Fig. 1). All patients had arthritis refractory to NSAID therapy for at least 3 months. The treatment protocol consisted of five consecutive infusions of the BP ibandronic acid. Dosage varied by age: 1.0 and 1.5 mg per infusion for children aged <7 and >7 years, respectively. The infusions were administered at 3-month intervals. BP therapy was integrated into a comprehensive rehabilitation plan that included therapeutic exercises, anti-inflammatory physiotherapy, and adherence to an orthopedic regimen, excluding axial loading on the affected limb. Therapy effectiveness and tolerance were evaluated through dynamic monitoring at 3, 6, 9, 12, and 18 months after treatment initiation. Clinical evaluation included physical examination of the patient, assessment of hip joint range-of-motion limitations, pain severity using the visual analog scale and Ritchie articular index, along with their changes over time [15].

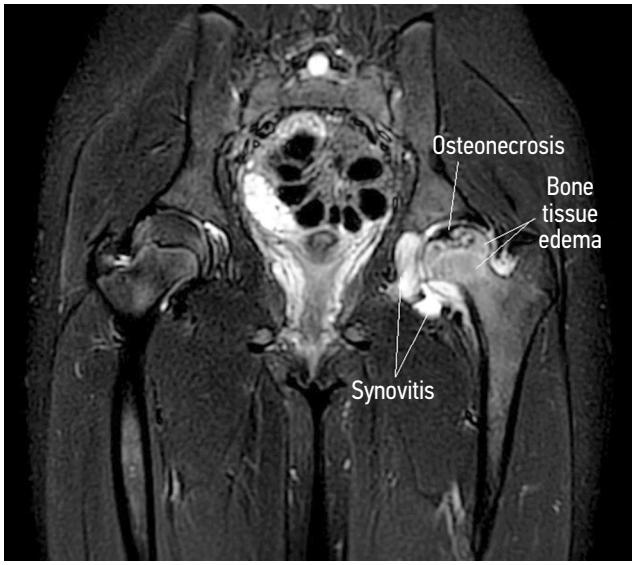

Fig. 1. Magnetic resonance imaging: stage II osteochondropathy of the left femoral head with signs of osteoarthritis. The short-tau inversion recovery mode revealed an extensive destruction zone in the femoral head, reactive trabecular edema in the head and neck, and signs of chronic synovitis

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Laboratory and instrumental diagnostic methods comprised the second component of the study protocol. X-ray imaging of the hip joints was performed in the anteroposterior and Lauenstein projections before treatment initiation and at 3, 6, 12, and 18 months of BP therapy. These radiographs determined the disease stage (classified by Reinberg) and assessed the femoral head morphology. The shape of the femoral head was evaluated using the ratio of its minimum to maximum radii, which was measured with a Mose template consisting of concentric circles spaced 2 mm apart. The template was aligned on an anteroposterior radiograph so that the smallest circle encompassed the contour of the femoral head. A ratio of >0.95 indicated a spherical cartilage model, 0.95–0.86 corresponded to grade I deformation, 0.85–0.76 to grade II, and ⩽0.75 to grade III. In addition, MRI was conducted every 3 months to evaluate osteoarthritis activity, calculate the necrotic lesion volume in the epiphysis, and assess the reactive bone marrow edema. Imaging was performed using a Philips Ingenia ElitionX 3-Tesla MRI scanner, with sequential visualization of the hip joints in T1 turbo spin echo and T2 STIR modes in the coronal, axial, and sagittal planes.

In addition to visual interpretation of the data, osteoarthritis activity was assessed using a modified SCORING OF HIP MRI FOR JIA scale adapted for children with LCPD [16]. This system was developed to analyze the inflammatory substrate in JIA that affects the hip joint and provides a sequential numerical assessment of the severity of synovitis, trabecular bone edema, erosive changes, and cartilage deformation. The modified scale for children with LCPD included a sequential assessment of inflammatory changes and femoral head involvement. Because true signs of JIA are absent in LCPD, erosive components and cartilage deformation of the femoral head were excluded from the evaluation.

The degree of synovial membrane thickening and effusion was determined to assess hip joint inflammation using the SCORING OF HIP MRI FOR JIA scale. Measurements were performed on T2 STIR images in the coronal plane by two radiologists. MRI inflammation markers were graded on a 0–3 scale: 0, no effusion or synovial membrane thickening; 1, minimal effusion within the joint capsule; 2, moderate synovial fluid accumulation stretching the joint capsule with synovial membrane reaction; and 3, significant synovial fluid accumulation stretching the joint capsule with synovial membrane proliferation (Fig. 2).

The severity of femoral head involvement was assessed based on the necrotic lesion volume and intensity of trabecular edema in the adjacent bone tissue and scored as

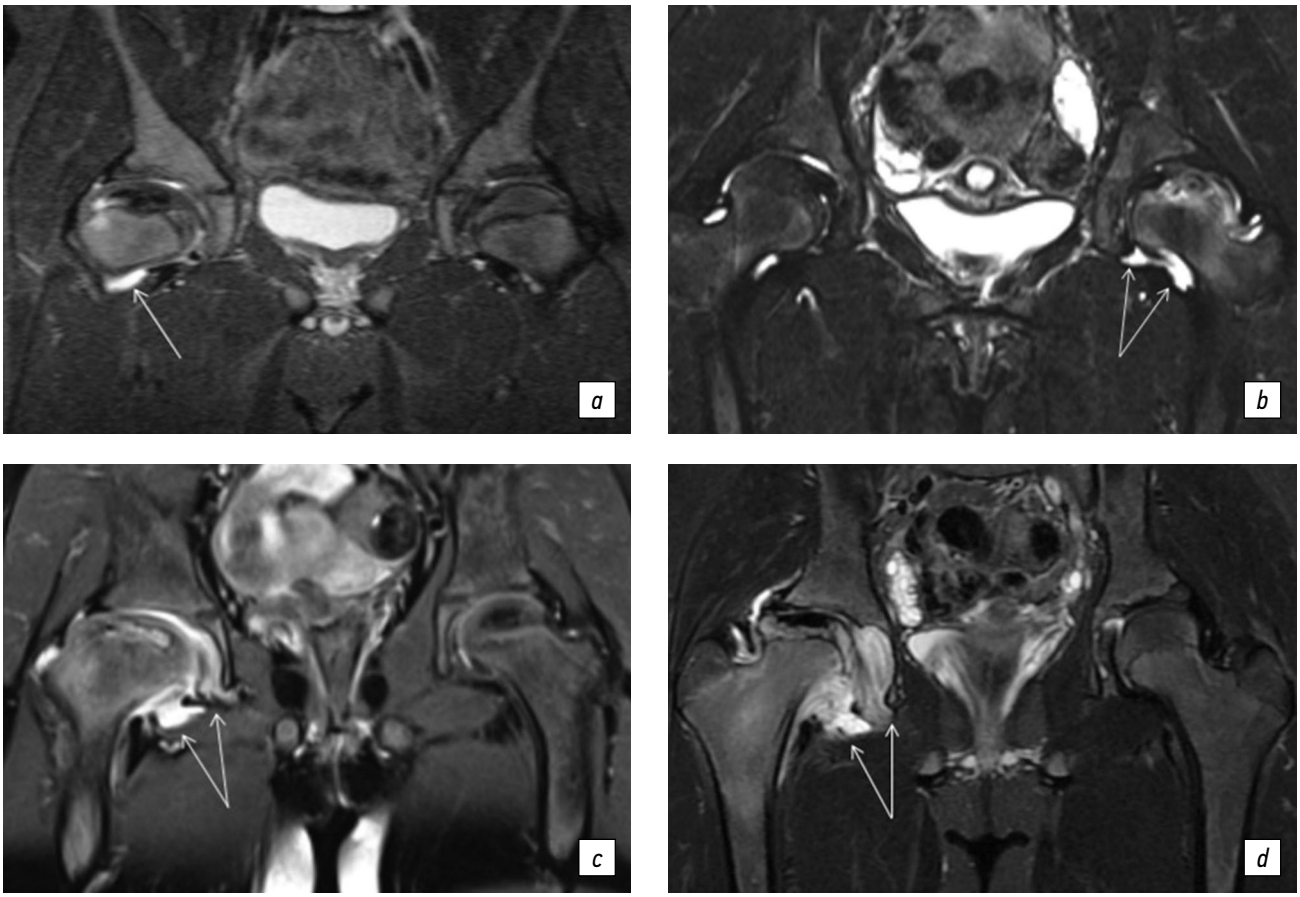

Fig. 2. Magnetic resonance imaging: signs of varying severity of synovitis in the hip joint in children with LCPD. STIR mode images show (*a*) minimal effusion within the joint capsule, (*b*, *c*) moderate synovial fluid accumulation stretching the joint capsule with synovial reaction, and (*d*) significant synovial fluid accumulation stretching the joint capsule with synovial proliferation

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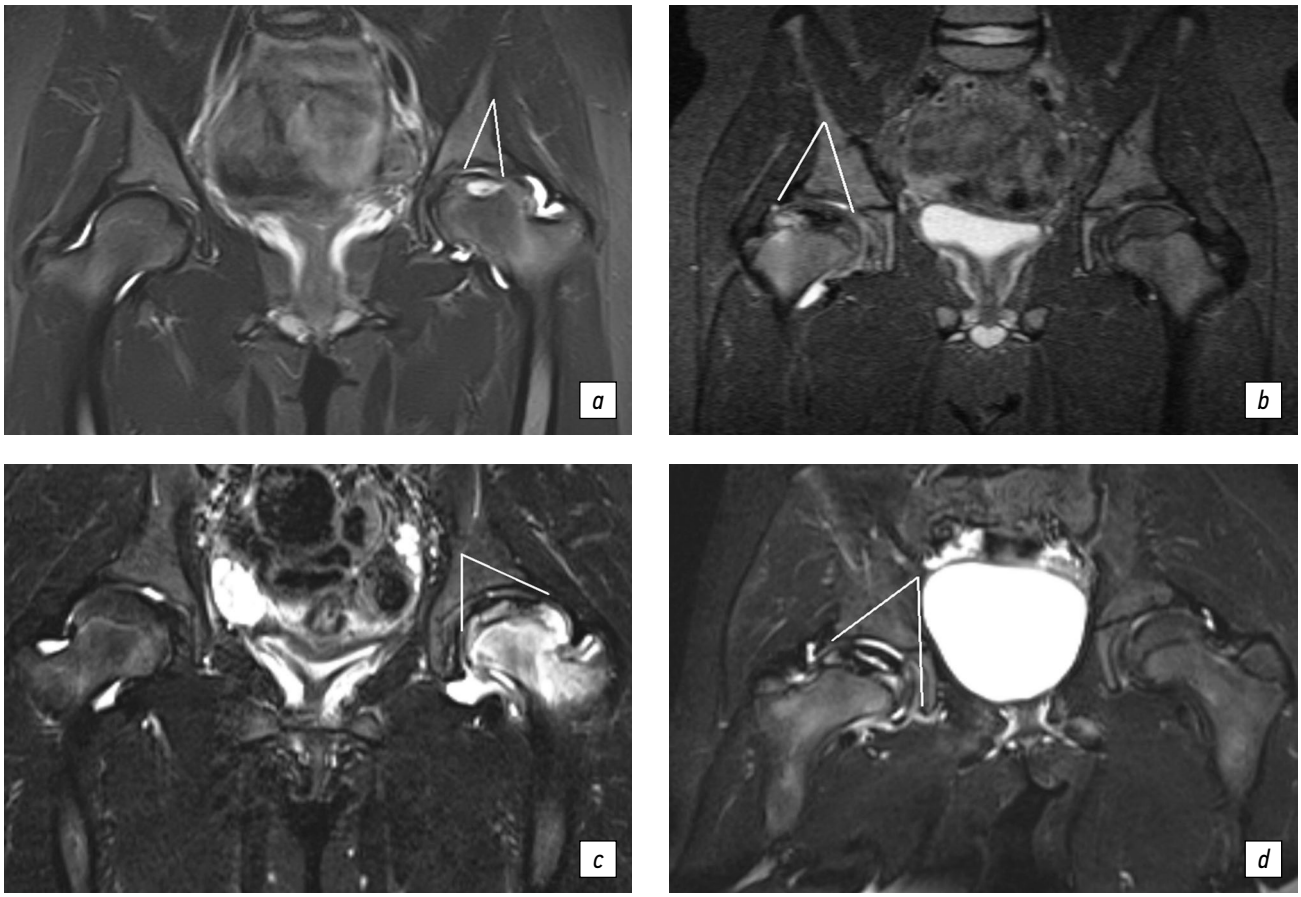

Fig. 3. Magnetic resonance imaging: signs of varying severity of femoral head lesions in children with the Legg–Calvé–Perthes disease. STIR mode images show (*a*) necrotic lesion and trabecular edema occupying ⩽33% of the epiphysis, (*b*) necrotic lesion and edema occupying 34%–66% of the epiphysis, (*c*, *d*) necrotic lesion and edema occupying 67%–100% of the epiphysis

follows: 0, no necrotic lesion or trabecular edema; 1, necrotic lesion and edema occupy ⩽33% of the epiphysis; 2, necrotic lesion and edema occupy 34%–66% of the epiphysis; and 3, necrotic lesion and edema occupy 67%–100% of the epiphysis (Fig. 3). The maximum total score was 6. The osteoarthritis activity levels were classified as follows: high activity, 5–6 points; moderate activity, 3–4 points; low activity, 2 points. Inactive stage: 0–1 point in the absence of a necrotic lesion (Fig. 4). The laboratory evaluation included the following parameters: standard inflammatory markers, bone metabolism markers, serum levels of calprotectin, vimentin, interleukin-6, and tumor necrosis factor-alpha, and titers of antinuclear factor using the HEp-2 cell line at the time of osteoarthritis diagnosis. In addition, all children were screened for antiphospholipid syndrome and hyperhomocysteinemia.

The study results were statistically processed using standard software, including the Microsoft Excel package.

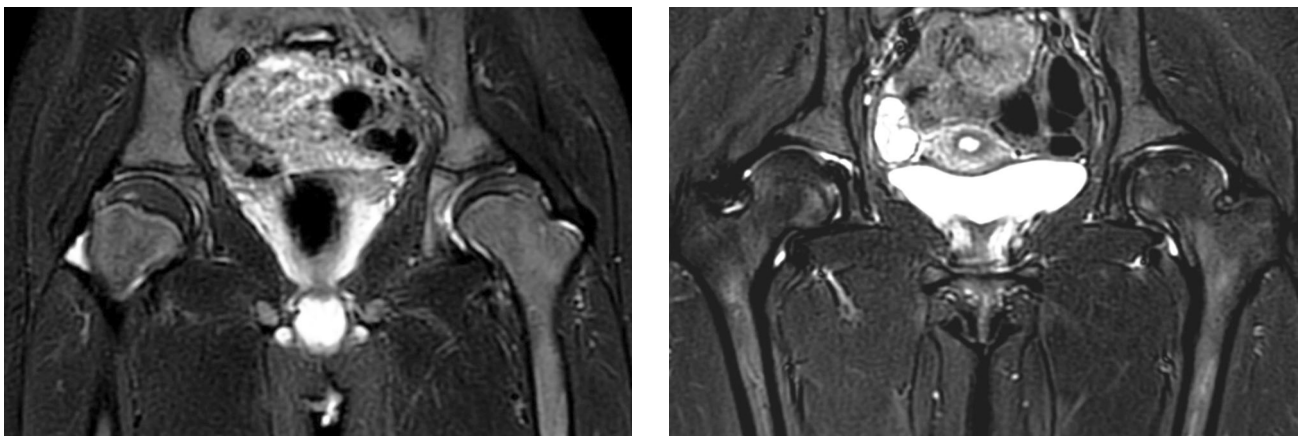

Fig. 4. Magnetic resonance imaging in the STIR mode: signs of the inactive stage of osteoarthritis in two children with left-sided Legg–Calvé–Perthes disease after bisphosphonate therapy

The comparative analysis of the empirical data were visually presented in a tabulated form. Absolute quantitative data are expressed as medians and interquartile ranges (*Me* [25; 75]). Relative data are presented as percentages. All patient representatives provided voluntary informed consent for study participation.

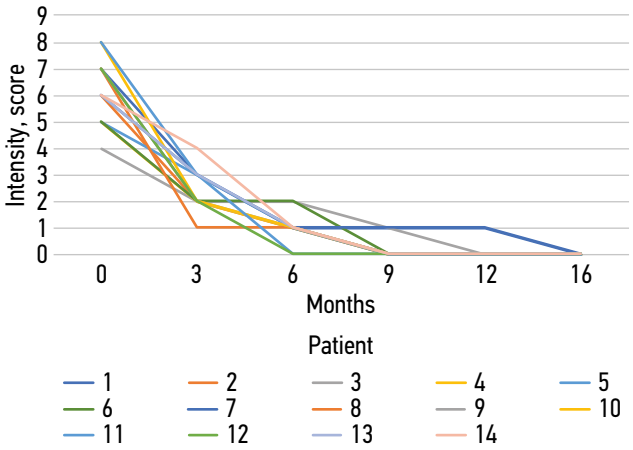

Fig. 5. Changes in pain reduction (visual analog scale, 10-point system) over time

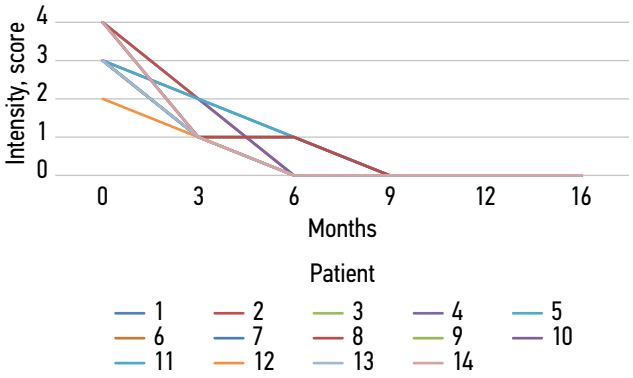

Fig. 6. Pain reduction dynamics (Ritchie articular index for the hip joint) (0, no tenderness during movement; 1 (mild pain), patient reports discomfort; 2 (moderate pain), patient reports discomfort and grimaces; 3 (severe pain), patient withdraws the limb)

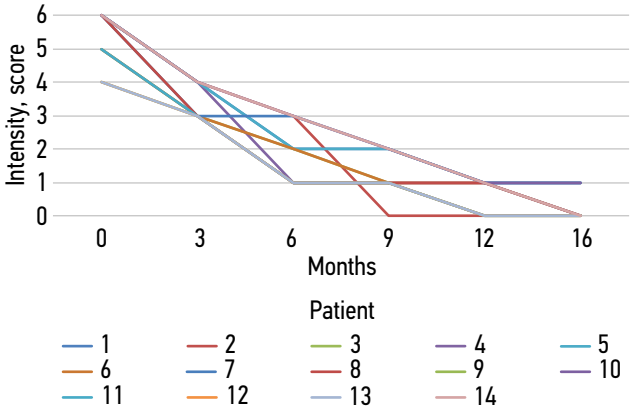

Fig. 7. Changes in osteoarthritis activity in children with the Legg–Calvé–Perthes disease during bisphosphonate therapy based on the modified SCORING OF HIP MRI FOR JIA Scale (0–6)

RESULTS

The effectiveness of BP therapy was evaluated in 14 children. Participants' age at disease onset ranged from 5 to 11 (mean, 7.5 ± 2.4) years. The average disease duration before osteoarthritis diagnosis and initiation of BP therapy was 14 [10; 22] months. The average follow-up period was 16 [12; 18] months, with a maximum duration of 24 months. Left hip joint ANFH was identified in 71.4% of the cases.

An inactive stage of osteoarthritis with BP therapy was achieved in 78.5% (11 children) after three consecutive infusions and 21.5% (3 children) after four infusions. Adverse reactions to transient post-infusion events, including arthralgia, dorsalgia, and febrile episodes, were observed in 87.5% (*n* = 12). These reactions occurred only after the first infusion and within 24–72 h. No other complications were reported. Pain relief was noted after the first infusion, with most children reporting no pain in the affected joint during active or passive movements by the third infusion (Figs. 5 and 6).

Pretreatment radiographs of the hip joints showed that all 14 patients were at the compression fracture stage according to Reinberg's classification. Femoral head deformation was observed in all cases: grade I deformation (mild), 71.4% (*n* = 10); grade II deformation (moderate), 28.6% (*n* = 4). No cases of grade III (severe) deformation were identified. Posttreatment radiographs after four consecutive infusions revealed the following stages: restoration stage, 71.4% (*n* = 10); fragmentation stage, 28.6% (*n* = 4). Despite the consistent use of abduction devices by all children, femoral head deformation slightly worsened: grade I, 50% (*n* = 7); grade II, 28.6% (*n* = 4); grade III (severe), 21.4% (*n* = 3), resulting in the subluxation of the affected joint. To stabilize the hip joint, three children with grade III underwent triple pelvic osteotomy.

At study enrollment, MRI findings indicated the following osteoarthritis activity levels based on the modified SCORING OF HIP MRI FOR JIA scale: high activity of hip osteoarthritis (5–6 points), 78.5%; moderate activity (4 points), 21.5%. Changes in the osteoarthritis activity during BP therapy are illustrated in Fig. 7.

At the time of osteoarthritis diagnosis, the inflammation parameters (C-reactive protein, platelet count, and white blood cell count) were within the reference ranges in all children. Serum levels of proinflammatory cytokines were also within normal limits. The mean erythrocyte sedimentation rate was 9 [5; 17] mm/h (Table 1). The titers of the antinuclear factor (ANF) determined in the assay using the HEp-2 cell line were significantly increased in 3 (21.4%) patients. No laboratory evidence of antiphospholipid syndrome or hyperhomocysteinemia was identified. At osteoarthritis diagnosis, 4 (28.5%) children showed 25-OH vitamin D

Table 1. Laboratory profile of inflammatory markers in children with the Legg–Calvé–Perthes disease and active osteoarthritis before and 6 months after bisphosphonate therapy

Parameter	Before bisphosphonate therapy	6 months after bisphosphonate therapy	Normal range
Erythrocyte sedimentation rate (mm/h)	9 [5; 17]	7 [3; 11]	0–15
C-reactive protein (mg/L)	0.62 [0.44; 0.99]	0.54 [0.32; 0.88]	0–5
Hemoglobin (g/L)	124 [112; 132]	122 [114; 130]	120–140
White blood cells ($\times 10^9$/L)	6.4 [5.2; 8.2]	6.8 [5.6; 8.8]	4.5–9.5
Platelets ($\times 10^9$/L)	332 [298; 345]	264 [206; 302]	180–410
Interleukin-6 (IL-6) (pg/mL)	3.6 [2.2; 4.4]	1.6 [0.7; 2.2]	0–7
Tumor necrosis factor-α (pg/mL)	0.65 [0.2; 0.85]	0.65 [0.2; 0.85]	0–7
Serum vimentin (pg/mL)	0.85 [0.4; 1.25]	0.85 [0.4; 1.25]	0–7
Serum calprotectin (μg/mL)	1.25 [0.75; 2.45]	1.25 [0.75; 2.45]	0–2.9
Antinuclear factor ⩾1/160 (%)	9 (64.3%)	–	<1/160
Antinuclear factor ⩾1/640 (%)	3 (21.5%)	–	<1/160

deficiency. After 6 months of BP therapy, the percentage increased to 7 (50%) children) (Fig. 8). By the end of therapy, only 3 (21.4%) children had persistent laboratory signs of 25-OH vitamin D deficiency. Among the bone metabolism markers, C-terminal telopeptide levels were high in 11 (78.5%) children during the active osteoarthritis phase with necrotic lesions. Most normalized within 6 months of BP therapy (Tables 2 and 3). The N-terminal propeptide levels required ongoing monitoring. By the end of BP therapy, N-terminal propeptide levels normalized in all children. No changes were observed in the alkaline phosphatase activity and electrolyte balance during BP therapy (Fig. 9). Other bone metabolism markers

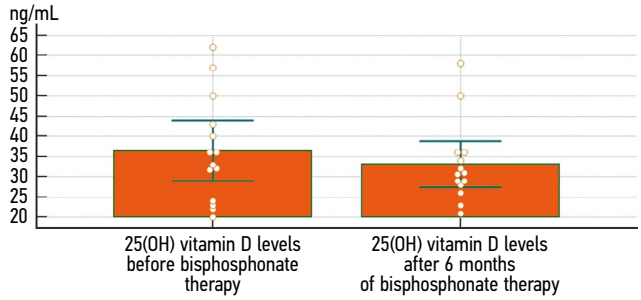

Fig. 8. Serum 25(OH) vitamin D levels in children with the Legg–Calvé–Perthes disease and osteoarthritis before and 6 months after bisphosphonate therapy

Table 2. Serum C-terminal telopeptide levels in children with the Legg–Calvé–Perthes disease and osteoarthritis before and 6 months after bisphosphonate therapy (ng/mL)

Patient	Age, years	Before bisphosphonate therapy	6 months after bisphosphonate therapy	Normal range*
1	8	1.74 (↑)	1.78 (N)	1.55–1.73
2	7	2.22 (↑)	1.88 (N)	1.55–1.73
3	9	2.42 (↑)	1.90 (N)	1.63–1.94
4	11	1.94 (↑)	1.84 (N)	1.01–1.81
5	12	2.26 (↑)	1.35 (N)	1.01–1.81
6	9	1.64 (N)	1.62 (N)	1.63–1.94
7	9	1.96 (↑)	1.88 (N)	1.63–1.94
8	8	1.84 (N)	1.84 (N)	1.63–1.94
9	12	1.53 (N)	1.64 (N)	1.01–1.81
10	8	1.82 (↑)	1.71 (N)	1.55–1.73
11	10	2.12 (↑)	2.02 (↑)	1.63–1.94
12	6	1.96 (↑)	1.44 (N)	1.55–1.73
13	10	1.98 (↑)	1.54 (N)	1.63–1.94
14	11	2.66 (↑)	1.64 (N)	1.63–1.94

*The reference values are based on data from the clinical diagnostic laboratory of the H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery.

Table 3. Serum N-terminal propeptide levels in children with aseptic necrosis of the femoral head and osteoarthritis before and 6 months after bisphosphonate therapy (ng/mL)

Patient	Age, years	Before bisphosphonate therapy	6 months after bisphosphonate therapy	Normal range*
1	8	556 (↓)	514 (↓)	584–738
2	7	654 (N)	628 (N)	584–738
3	9	517 (N)	586 (N)	388–571
4	11	537 (N)	465 (N)	207–597
5	12	467 (↑)	424 (↑)	109–267
6	9	381 (↓)	612 (↓)	670–1042
7	9	458 (↓)	726 (N)	670–1042
8	8	428 (N)	480 (N)	388–571
9	12	440 (N)	612 (N)	207–597
10	8	560 (↓)	580 (↓)	670–1042
11	10	456 (↓)	634 (↓)	737–1103
12	6	602 (N)	536 (↓)	584–738
13	10	870 (N)	900 (N)	737–1103
14	11	278 (↓)	415 (↓)	737–1103

*The reference values are based on data from the clinical diagnostic laboratory of the H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery.

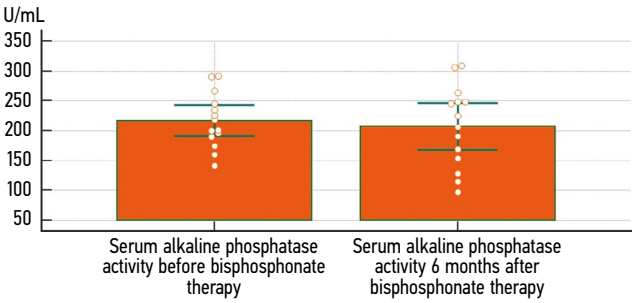

Fig. 9. Serum alkaline phosphatase activity in children with the Legg–Calvé–Perthes disease and osteoarthritis before and 6 months after bisphosphonate therapy

in children with LCPD before treatment initiation and after a long period of BP therapy remained within the reference ranges throughout the study.

DISCUSSION

The use of drug products that inhibit osteoclast hyperactivity in children represents a novel approach to LCPD with osteoarthritis symptoms. BP therapy in children with LCPD appears promising and opens new opportunities for disease management.

To date, no studies have evaluated the efficacy of BP therapy in children with LCPD. Thus, this study aimed to optimize conservative therapy for osteoarthritis in children with LCPD. The treatment outcome analysis conducted at the H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery revealed that LCPD with significant inflammatory processes at the early stages was associated with increased necrotic lesion volume in the epiphysis and characterized by a torpid course. Synovitis often precluded timely surgical intervention, and without adequate treatment, this disease variant inevitably led to severe joint structure deformation and subluxation. The low efficacy of NSAIDs necessitated alternative anti-inflammatory agents. The therapeutic model was adapted from adult treatment protocols for idiopathic ANFH and involved short-term BP therapy [17]. Furthermore, this study was initiated given the high efficacy of BP therapy in children suffering from nonbacterial osteomyelitis, a condition characterized by uncontrolled osteoclast hyperactivity that results in bone tissue destruction [18]. Ibandronic acid was selected based on promising experimental and clinical data demonstrating its ability to restore the nanomechanical properties of the anatomical structure of the femoral head following ischemic osteonecrosis [19]. The dose, duration, and safety monitoring complied with the clinical guidelines of the European Society of Rheumatology for the treatment of nonbacterial osteomyelitis in children (CARRA, 2017, 2019) [20].

CONCLUSION

The proposed BP therapy for children with LCPD is advantageous because it not only reduces inflammation and osteoclast activity but also prevents further progression of femoral head deformation. Importantly, BP therapy does not involve rheumatology specialists and can be implemented in pediatric trauma and orthopedic departments.

The preliminary results on the efficacy and safety of the therapy highlight its potential in the comprehensive treatment of children with LCPD and osteoarthritis. However, given the small sample and short observation period, further detailed investigations and analyses are necessary to confirm the long-term effects of BP therapy.

ADDITIONAL INFORMATION

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Competing interests. The authors declare that they have no competing interests.

Ethics approval. The protocol for the examination and treatment of children was approved by the Local Ethics Committee and the Scientific Board of the H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Ministry of Health of Russia (Protocol No. 8, December 2021).

Consent for publication. Consent was obtained from the patients and their representatives for participation in the study and publication of data.

Author contribution. All authors made a significant contribution to the study and preparation of the article, and each read and approved the final version before it was published.

The major contributions were distributed as follows: *A.N. Kozhevnikov* developed the concept and study design and wrote the manuscript; *D.B. Barsukov* conducted the interim manuscript editing, collected and analyzed data; *P.I. Bortulev* conducted the interim and final manuscript editing, collected and analyzed data; *S.A. Braylov* conducted interim manuscript editing and collected and analyzed data.

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